1-11 and 13-26 have been cancelled by the present amendment. Claim 27 has been amended, and new claims 28-52 have been added. The new claims and the amendment of claim 27 are fully supported throughout the specification, including the claims as originally filed, and do not add new matter. In order to avoid any ambiguity, the claims now recite "DM2" proteins instead of "MDM2" whenever reference to a genus, including both murine and human DM2, is intended. Support for this language is at least at page 2, lines 11-13 of the specification.

Turning now to the rejections set forth in the Office Action mailed on March 13, 2001 (Paper No. 16), applicants submit the following arguments for the Examiner's consideration, where reference is made to the numbering used in the Office Action.

Re. 4 In view of the numerous amendments requested in the Preliminary Amendment filed on March 26, 1999, applicants were invited to submit a substitute specification under 37 C.F.R. § 1.121. A substitute specification is being prepared and will be submitted shortly.

Re. 5 A reference to the PCT application underlying the present national phase filing, as well as to two United Kingdom priority applications, has been inserted into the specification, as requested.

Re. 6 Claims 22 and 25 were objected to under 37 C.F.R. § 1.75(c) as "being in improper dependent form." Claims 22 and 25 have been cancelled, which moots their rejection. It is believed that all newly submitted claims are in proper dependent form and should not raise any similar issues.

Re. 7-8 Claim 13 was rejected under 35 U.S.C. § 101 for its recitation of a use, without setting forth any steps involved in the process. The cancellation of claim 13 obviates this rejection. As the newly submitted claims do not recite a use without the recitation of appropriate process steps, applicants do not anticipate a similar rejection of any of the current claims.

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Re. 9-10 Claims 14, 15, 17, and 23 were rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement.

Specifically, claim 14 was rejected for being "broadly drawn to a pharmaceutical composition for the treatment or prevention of an unspecified disease that responds in an unspecified manner to the inhibition of the interaction of p53 and MDM2," and for including the recitation of "an unspecified derivative" of the peptides characterized by the presence of a consensus sequence and a functional limitation. Claim 15, a method claim drawn to the preparation of a pharmaceutical composition in a "method of use" format, and Claim 17, drawn to a method of treatment or prevention, were rejected for similar reasons. In analyzing the *In re Wands* factors, the Examiner refers to difficulties known in the art concerning the successful therapeutic application of peptides that affect targets within the cell, the "limited guidance" in the specification, characterized as "cursory" which "does not go beyond what was already known in the art at the time the invention was made," and the alleged lack of working examples "that are reasonably expected to correlate with the successful therapeutic application of the invention." From this, the Examiner concludes that the practice of the invention claimed in the rejected claims would require undue experimentation, which would be "extensive and of trial-and-error nature." In rejecting claim 23, the Examiner additionally notes that the claim embraces "the therapeutic application of gene therapy to deliver a nucleic acid expressing the peptide of the invention, . . . and the therapeutic application of antisense or triplex-forming (antigene) oligonucleotides." The Examiner refers to the "relatively undeveloped" nature of the state of the gene therapy, antisense, and antigene arts, the "inconsistent results" reported, technical difficulties, such as "the lack of suitable vectors" and the "inadequate understanding of the biological interaction of these vectors with the host." With regard to the application of oligonucleotide therapeutics, such as antisense and antigene oligonucleotides, the Examiner cites Stull et al. as teaching "several formidable obstacles" associated with the development of nucleic acid therapeutics. Finally, the Examiner notes that the gene therapy art is unpredictable. From this, the Examiner concludes that it would require undue experimentation to practice the invention defined in claim 23.

The cancellation of claims 14, 15, 17, and 23, which was done without prejudice and without acquiescence in the Examiner's position, obviates the rejection of these claims.

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Newly added claims 47 and 49, drawn to subject matter somewhat similar to original claims 1, 15 and 17, should not receive an analogous rejection. Claims 47 and 49 do not concern the treatment of an unspecified (or specified) disease nor do they recite derivatives of the peptides characterized by structural and functional features, therefore, the first part of the rejection does not apply. As to the difficulties associated with the ability of the peptides to reach their intracellular target, applicants refer to the teaching of Example 10, providing detailed methods to improve the intracellular stability and facilitate cellular uptake of the peptides of the invention. Indeed, the results set forth on pages 39-40 demonstrate successful delivery of a binding element (TIP 12/1) comprising the peptide insert of clone 12/1 described in Example 8 by intranuclear injection, as shown by induction of the p53 reporter in MCF-7, U2-OS and OSA cells.

Nor should newly added claim 49 be rejected on similar grounds. Claim 49 concerns a method for inducing growth arrest or apoptosis in a tumor cell by introducing into the cell a DNA molecule which expresses a peptide of the invention. This application of gene therapy does not raise the same issues as those discussed in the Office Action and the cited references. For example, gene therapy, as discussed in the "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy" (1995) cited in the Office Action, is somatic gene therapy that requires transfer of DNA into recipient cells, "where it will reside for a prolonged period." (Page 7, last paragraph.) The method defined in claim 49 aims at arresting the growth of or killing tumor cells. In order to achieve this goal, it is sufficient that the DNA in delivered to the target tumor cell where it exerts the requisite biological activity, it is not required to stay within the cell for a prolonged period.

Re. 11 Claims 18-22 were rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement, "because the specification, while being enabling for inhibiting the interaction between MDM2 and p53 *in vitro*, does not reasonably provide enablement for inhibiting the interaction *in vivo*." The Examiner, again, refers to the difficulties associated with the therapeutic application of nucleic acids, which are held "not enabled" for reasons set forth in support of the foregoing rejection. Claims 18-22 are cancelled, which moots their rejection. None of the newly added claims should be rejected on similar ground for reasons discussed above in response to the similar rejection of claims 14, 15, 17, and 23.

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Re. 12-13 Claims 1, 3, 6-8, 10, 11, 14-17, and 24 were rejected under 35 U.S.C. § 112, second paragraph, as "indefinite" in their recitation of the phrase " . .. capable of binding . . . (claims 1, 10, 11, 16, 17, and 24), or for using the language "preferably" (claims 3, 7, 8, 10, 11, 14, 15, and 17). As the rejected claims have been cancelled and the new claims do not contain the language objected to, the Examiner is requested to withdraw this rejection.

Claim 6 was further rejected for reciting a fragment comprising "at least 8 consecutive amino acids," in contrast to the peptide of formula (I) which was required to contain at least 10 consecutive amino acids. Claims 7 and 8 were rejected for the same reason. Claims 6-8 have been cancelled, and claim 27 recites that the claimed compound comprises at least eight consecutive amino acids of formula (I). Accordingly, none of the new claims should be rejected for a similar reason.

Claim 13 was rejected for being in a "use" format without reciting any method/process steps. Claim 15 was rejected on a similar ground. Claims 13 and 15 have been cancelled. Since all pending method claims positively recite method steps, they should not be subject to a similar rejection.

Claim 11 was held indefinite for "reciting a broad range or limitation together with a narrow range or limitation." The cancellation of claim 11 obviates its rejection, and the pending claims do not contain the structure objected to.

Claim 22 was rejected as "indefinite because it depends from both claim 21 and claim 1, leaving unclear from which claim it is intended to depend." Claim 22 is cancelled, and the pending claims do not raise this issue.

Re. 14-15 Claims 1, 2, 18-22 and 24-26 were rejected under 35 U.S.C. § 102(e) "as being anticipated by Burrell et al. (US Patent No. 5,420,263)."

Claims 1, 2, 18-22 and 24-26 have been cancelled, without prejudice, and without acquiescence in any grounds for their rejection. The claims currently pending are clearly not anticipated by Burrell et al.

Burrell et al. is directed to nucleic acid probes and primers for diagnosing and detecting neoplasmic tissue, and MDM2 gene amplification. The Examiner has highlighted three passages from the Burrell et al. patent: (1) column 6, lines 44-52, which discloses oligonucleotides that

bind to the mdm2 gene or mRNA; (2) column 6, lines 58-64, which discusses small molecules, peptides and antibodies which can inhibit the binding of MDM2 to p53 (with reference to lines 53-57); and (3) column 7, lines 9-37, where the use of p53 derivatives is suggested for binding to excess MDM2 in cells where MDM2 is over expressed.

The only small molecules disclosed by Burrell et al. are peptides which have the consensus sequence TFSDLW, which differs from the consensus sequence present in the peptides of the present invention, which recites H, F, or Y in place of L in the above formula. Accordingly, the claims are not anticipated by Burrell et al.

In addition, in column 7, lines 9-19, Burrell et al. teaches that amino acid residues 13-41 of p53 (SEQ ID NO: 1) "are necessary for the interaction of MDM2 and p53. However, additional residues on ether the amino or carboxy terminal side of the peptide appear also to be required. Nine to 13 additional p53 residues are sufficient to achieve MDM2 binding, although less may be necessary." In view of this teaching, applicant's finding that an eight amino acid consensus sequence is sufficient for MDM2 binding is unexpected. As a result, Burrell et al. should not be cited as making obvious any of the claims pending in the present application.

Re. 16 Claims 1-8, 10, 11, 18, 21, 22 and 24-26 were rejected under 35 U.S.C. 102(e) "as being anticipated" by Picksley et al. (either one of US Patent Nos. 5,792,908 and 5,770,377). Picksley et al. is cited for its teaching of fragments of human p53, and in particular peptides of 6, 7, 10 and 15 residues (SEQ ID NOs: 2, 26, 27, 1 and 6, respectively in the '908 patent). These sequences comprise a consensus sequence similar to the sequence shown in formulae (I), (Ib), and (Ic), with the exception that in Picksley et al. R3 is the amino acid leucine (L). According to the Examiner the reference to "derivatives" in the claims encompassed peptides including the consensus sequence of Picksley et al.

All rejected claims are now cancelled, without prejudice, and without acquiescence in their rejection. Since the claims currently pending no longer refer to derivatives, any issues of potential anticipation by Picksley et al. are moot.

Re. 17-18 Claim 16 was rejected under 35 U.S.C. § 103(a) "as being unpatentable" over Picksley et al. (US Patent No. 5,702,908) "in view of what is known in the prior art for the reasons set forth in the Office action mailed 7/3/00." Picksley et al. was cited for its teaching of

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fragments of human p53 that bind to human MDM2 to inhibit binding of p53 to MDM2, as well as for its disclosure of the preparation of peptide fragments using recombinant DNA techniques.

According to the rejection, it would have been obvious to synthesize peptides as claimed in claim ~~18~~ 16 in view of Picksley et al. and further in view of general knowledge in the art about preparation of peptides by chemical synthesis. As claim 16 has been cancelled, and the pending claim set does not contain a corresponding claim, the present rejection is moot. It is noted, however, that since the peptides of the present invention are novel and unobvious, their preparation by any method, including recombinant DNA technology and chemical synthesis, is also unobvious.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: September 28, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The following sentence has been added on page 1, following the title:

--This is a U.S. national phase filing of PCT Application No. PCT/EP97/03549, filed on July 4, 1997, the disclosure of which is hereby expressly incorporated by reference in its entirety.--

In the Claims:

Claims 28-52 have been added.

Claim 27 has been amended as follows:

27. (Once amended) A compound which binds to [MDM2] a DM2 protein, [wherein the compound inhibits the binding of MDM2 to p53] which compound comprises an amino acid motif comprising at least eight consecutive amino acids of the formula

R_1-X-F-X-R_2-R_3-W-X-X-R_4 (I) (SEQ ID NO: 4)

wherein

R_1 is a proline (P), leucine (L), glutamic acid (E), cysteine (C) or glutamine (Q),

X stands for [one (any)] any natural amino acid,

R_2 is arginine (R), histidine (H), glutamic acid (E), cysteine (C), serine (S), or aspartic acid (D),

R_3 is histidine (H), phenylalanine (F) or tyrosine (Y),

R_4 is phenylalanine (F), glutamine (Q) or leucine (L); and

F is phenylalanine and W is tryptophan,

and inhibits the binding of said DM2 protein to a p53 protein.

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